A Sequenced Strategy for Improving Outcomes in People With Knee Osteoarthritis Pain

Master Consent Form Phase 1 Version 2.4

NCT04504812

March 14, 2022

Participant Study ID _____

RESEARCH PARTICIPANT INFORMED CONSENT AND PRIVACY AUTHORIZATION FORM

Protocol Title: A sequenced strategy for improving outcomes in people with knee osteoarthritis pain (SKOAP)

Phase 1 Consent

JHM IRB Application No.: IRB00238678

Version Number and Date: Version 2.4 March 14th, 2022

Sponsor/Supporter/Funded By: National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

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See "Study Site Information" at the end of this consent form for contact information about your local study team.

You are being asked to join a research study. Participation in this study is voluntary. Even if you decide to join now, you can change your mind later.

This study is a multi-site study, meaning it will take place at several different places. Because this is a multi-site study, this informed consent form includes two parts. The first part has information that applies to all places. The second part has information for the place where you are being asked to enroll.

1. Research Summary (Key Information):

The information in this section is intended to be an introduction to the study only. Complete details of the study are listed in the sections below. If you are considering participation in the study, the entire document should be discussed with you before you make your final decision. You can ask questions about the study now and at any time in the future.

This study compares different non-surgical treatments for knee pain due to osteoarthritis. There are 2 phases in the study. Today we will discuss Phase 1 of the study. If you are not interested in enrolling in Phase 1, a study team member may talk with you about Phase 2. Phase 2 is described in detail on a separate consent form. Phase 2 involves treatments that are more invasive than the treatments described below. Please tell the study team if you would like to learn more about Phase 2.

For people who enroll in Phase 1, a computer will determine in which one of the following 3 groups you will be placed:

1. **Best Practices** includes treatments that experts recommend for knee arthritis pain. Best Practice can include topical or oral pain relievers, a structured exercise program, and weight management if your BMI is over 30. Other non-invasive treatments such as acupuncture, yoga, and physical therapy are also included.

2. **Best Practices** + **duloxetine**
   Duloxetine is a drug that is used to improve pain and function in people with knee osteoarthritis (KOA). Duloxetine is approved by the Food and Drug Administration (FDA) for the treatment of depression, anxiety disorder, fibromyalgia, and joint pain, such as KOA. We are not testing whether duloxetine works, but rather how it compares to other treatments.

3. **Best Practices** + **duloxetine + web-based pain coping skills training**
   The web-based pain coping skills training is an 8-week enhanced web-based system that includes a manual, videos, skills training, and homework/practice assignments to reduce knee pain and improve functioning. The program guides people through methods of relaxation, using positive thoughts, pleasant activity scheduling, replacing negative thoughts, pleasant imagery, and problem solving to decrease pain. Participants are encouraged to watch modules weekly (approximately 45 minutes each), set goals for practice and track their practice techniques daily. If you get assigned to this condition, we will give you more information and instructions for logging in and how to use the program.

As part of the study, you will have a telemedicine visit at four (4) and eight (8) weeks after the baseline visit, or these visits may be conducted at the clinic if needed. After that, you will be contacted each month. These contacts will continue for as long as 2 years.

You will complete a confidential contact form and you will choose if you prefer this contact to be online, text, email, or by telephone. There are risks to the study procedures and the study drug that are described later in this document.

2. Why is this research being done?

This research is being done to compare treatments for knee osteoarthritis pain.

Knee osteoarthritis (KOA) occurs when the cartilage that cushions your knee joint wears down over time or from trauma. Symptoms of KOA include pain, swelling, tenderness, stiffness, and loss of flexibility in the knee. People with KOA pain are often treated with opioids, which can lead to opioid addiction. In this study, we are comparing non-opioid treatments in an effort to lessen your pain and improve knee function.

Are there any investigational drugs/devices/procedures?

None of the Phase 1 treatments are experimental. They are commonly used for knee osteoarthritis pain.

Who can join this study?

People 18-90 years of age with knee osteoarthritis pain, and without knee replacement in the painful knee joint, may join. Study participants will need to be comfortable using a computer for simple tasks.

How many people will be in this study?

This is a multicenter study. We expect about 1500 people to be enrolled in Phase 1. About 300-500 people will enroll in each of the 3 groups.

3. What will happen if you join this study?

If you agree to be in this study, we will ask you to do the following things:

Baseline Visit

During this visit, you will review and provide written consent to participate. By signing, you are providing your permission to allow our study team access to your medical records. This information will include x-rays, CT, or MRI scans, as well as other details from your medical record.

We will ask questions concerning your medical history, general health, pain, physical function, and how you feel mentally or emotionally. We will also ask questions about your medications (including opioid use), drug allergies, and contraindications for duloxetine. The answers will be recorded on a paper form or directly into an electronic system.

A brief examination of the affected knee will be performed by a member of the study team.

Women who can bear children will be asked to confirm that they are not pregnant or lactating and using reliable birth control. They will also be asked to notify the research staff if they become pregnant at any point during the study period.

The baseline visit will take approximately 1-3 hours.

Randomization

A computer will randomly (like drawing numbers from a hat and) assign you to one of three groups as listed below: You will have an equal chance of being in any one of the 3 study groups.

1. *Best Practices*

   The **Best Practices Group** will continue or begin standard treatments as recommended by your doctor, such as those listed below. Best practices not listed below may be discussed between you and your doctor. The study does not pay for best practice options (see section 9).

   Best Practices Treatment Options

   - Topical (on the skin) or oral (by mouth) non-steroidal anti-inflammatory drugs (NSAIDS), such as ibuprofen (Advil®, Motrin®)
   - Acetaminophen (Tylenol®)
   - A structured exercise program and/or physical therapy
   - Biomechanical knee braces, canes, or kinesiotaping
   - Weight management if your BMI is over 30
   - Acupuncture
   - Yoga or Tai Chi
   - Other non-invasive treatments for knee pain

If you have already been taking a stable dose of opioid medication for two weeks or more, you may continue using this medication. While you are in this study, we recommend that your opioid dose is not increased. Common opioids would include medications containing oxycodone, hydrocodone, hydromorphone, morphine, and tramadol.

You will receive treatments in the **Best Practice** group for 8 weeks. After 8 weeks, we will ask about your pain and function. At that time, you may choose to maintain your current therapy. Or you can be re-randomized (like a flip of a coin) into the other study groups. We will ask about your pain and work with you to decide if you would like to receive additional treatment.

2. *Best Practices + duloxetine*
In this group, you will receive best practices and duloxetine, an oral (by mouth) medication used for chronic joint pain.

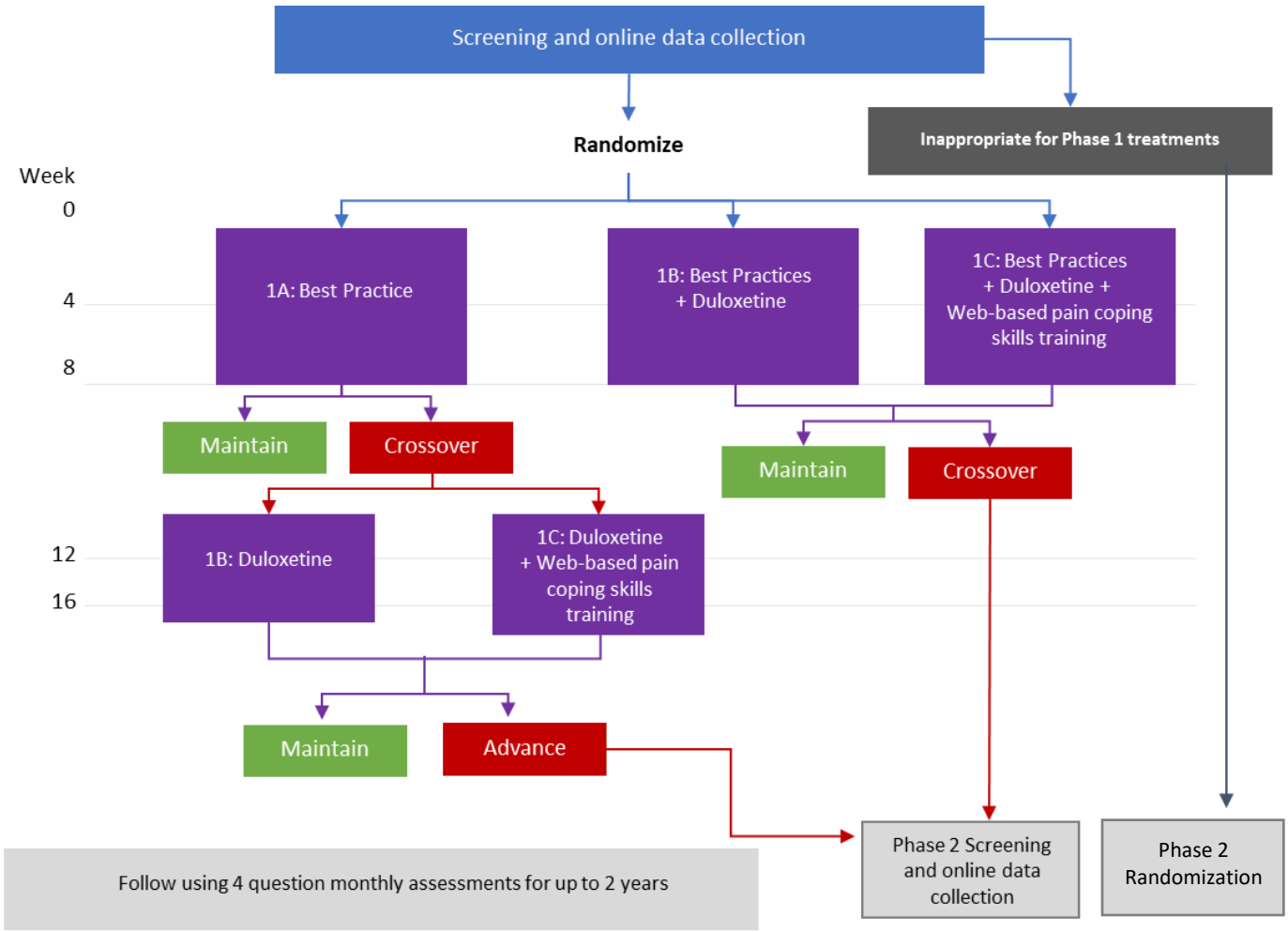
   Duloxetine is a serotonin and norepinephrine (brain chemicals) reuptake inhibitor. Duloxetine is a pill taken by mouth with or without food and is stored at room temperature. Duloxetine will be prescribed by a study team member. We ask you to fill the prescription as soon as possible. The dose will be tailored to you and will be adjusted as needed over the course of the study. A study team member will contact you in about 2 weeks to check in and see how taking duloxetine is going for you.

   You will receive **Best Practices + duloxetine** for 8 weeks. After 8 weeks, we will ask about your pain and function. We will work with you to decide if you would like to receive additional treatment as part of Phase 2 of the study.

3. *Best practices + duloxetine + web-based pain coping skills training*
In this group, you will receive best practices, duloxetine as described above, and online training in pain management techniques.

   The web-based pain coping skills training is an 8-week web-based system that teaches you relaxation and coping skills to effectively manage your pain. The system includes a manual and online videos and skills training. The system helps you try out these skills during your daily life by sending email or text reminders for you to practice what you have learned. A member of our study team will contact you if you have trouble working with the program.

   You will receive **Best Practices + duloxetine + web-based pain coping skills training** for 8 weeks. After 8 weeks, we will ask about your pain and function. We will work with you to decide if you would like to receive additional treatment as part of Phase 2 of the study.



Follow Up Visits

Subsequent Visits

As part of the study, you will have a phone call or telemedicine visit at four (4) and eight (8) weeks after today's baseline visit, or have an in- person clinic visit if required. During these visits, we will ask you about your current medications, pain level, physical function level and any issues you are having with your current treatment. The study doctor may adjust your treatment at these visits. There will also be some questionnaires to complete related to your experience of pain. The 4-week visit will take approximately 30 minutes. The 8-week visit will take approximately 60 minutes.

Monthly Follow Up Contact

After the 8-week visit, we will contact you each month by your choice of an online survey, text, email or telephone. You will be asked questions related to how you feel and about any current therapy or surgery related to your knee osteoarthritis. These follow up contacts take approximately 10 minutes. We will contact you every month for a maximum of two years.

You will be contacted primarily by phone, but may also be contacted by email or postal mail by trained research staff from the Economics and Patient Reported Outcomes Center at Duke Clinical Research Institute (the DCRI Call Center) if you choose to be contacted monthly by phone, or if you miss a text/online monthly follow-up. The research staff will call you on the numbers you provided. Once enrollment is completed at your site, your site may close. If so, you may be followed by the DCRI Call Center. You will be notified if your site closes.

Web Based Coping Skills Training Follow Up Contact
A trained coping skills facilitator will contact you using the number and/or email address you provided if you are randomized to the Best Practices + duloxetine + web-based pain coping skills training group. They will contact you to help you get registered if needed. If you do not finish a lesson in seven days, the facilitator will contact you using the number or email you provided. You may also receive communication from the facilitator if you have not started a module ten days after your last module ended or if you are moving through the modules too quickly. You may also set up automated reminders that can text or email you.

Will research test results be shared with you?
We will share with you only results that may impact your medical care.

How long will you be in the study?
You will be in Phase 1 of this study for a maximum of 36 months. There will be 3 visits for most people and then monthly contact (online/telephone). For those in Best Practices that would like additional treatment, you can be re-randomized to one of the other two groups.

4. What happens to data that are collected in the study?

Our research team works to advance science, clinical practice, policy and public health. The data we collect about you are important to this effort.

If you join this study, you should understand that you will not own your research data. If researchers use your data to create a new product or idea, including those that may have commercial value, you will not benefit financially from those efforts.

How will your data be shared now and in the future?
Sharing data is part of research and may increase what we can learn from each study.

Often, data sharing is required as a condition of funding or for publishing study results. It also is needed to allow other researchers to validate study findings and to further research.

Your data may be shared with:

- Johns Hopkins University, as the core study team
- University of Utah, as the study database manager
- Duke University, as the clinical coordinating center
- Duke Clinical Research Institute Call Center
- research collaborators, other researchers, sponsors, government agencies, publishers of papers and other research partners
- federal government or other databases/repositories

Data sharing could change over time, and may continue after the study ends.

We will do our best to protect and maintain your data in a safe way. An Institutional Review Board (IRB) is a group of people that reviews human research studies. Generally, if we share your data without identifiers (such as your name, address, date of birth) no further review and approval will be needed. If data are shared with identifiers, further Institutional Review Board (IRB) review and approval may be needed. The IRB will determine whether additional consent is required.

The use of your data is required for participation in this research study. If you are not comfortable with the use of your data in future research without further consent, you should not participate in this study.

5. What are the risks or discomforts of the study?

There is a risk that you may be randomized to a study arm that is not as effective as you would like or as effective as another arm offered in the study.

Risks from duloxetine

- Common side effects (5-15 in 100 people)
  - Constipation
  - Nausea
  - Fatigue
  - Decreased appetite
  - Dry mouth
  - Excessive sweating

- Uncommon side effects (less than 5 in 100 people)
  - Dizziness, fainting, or falls
  - Sleepiness or drowsiness
  - Diarrhea
  - Shortness of breath

- Serious but rare side effects (less than 1 in 100 people)
  - Liver function test elevation and/or jaundice (see more information below)
  - Psychiatric symptoms (worsening depression, suicidal thoughts, anxiety, agitation, panic attacks, aggression and anger)
  - Low blood sodium level
  - Severe skin reactions (blisters, peeling rash, or mouth sores)

Suicidal Thought and Behavior: Some people (less than 1 in 100 people) have thoughts of suicide or suicidal behavior when first taking duloxetine. Report any new or worsening symptoms or mood changes to your study team contact and your healthcare provider.

Serotonin Syndrome: Duloxetine may cause a serious side effect called Serotonin Syndrome when used with other medications. These include:

- MAO Inhibitors (a class of medications used to treat depression, panic disorder, and Parkinson's disease)
- Some other medications or herbal products used to treat depression, Parkinson's disease, or migraine headaches.

Symptoms include high fever, agitation, hallucinations, coma, fast heart rate, flushing, tremor, sweating, dilated pupils, and diarrhea. Treatment may require hospitalization.

Duloxetine should not be taken within five days before or 14 days after you have used an MAO Inhibitor. To minimize this risk, prior to starting duloxetine we will ask about your recent and current medications and over the counter products, in addition to your medical history.

Liver Failure: There have been reports of liver failure, **sometimes fatal**. Report any new or worsening symptoms of abdominal pain, abdominal enlargement, or yellowing of the skin or eyes to your study team contact and your healthcare provider.

Drinking alcohol while using duloxetine can increase the risk of severe side effects, including liver damage/failure and symptoms of depression.

As part of our initial assessment, we will try to make sure you do not have conditions that predispose you to severe side effects, including conditions such as advanced liver and kidney disease, seizures, bleeding problems, glaucoma, bipolar, drug addiction, or suicidal thoughts.

To minimize risks, report any new or worsening conditions to your study contact and your healthcare provider.

To avoid side effects, duloxetine must be gradually tapered. Do not stop using duloxetine without first speaking with the study team contact and your healthcare provider.

Risks from the web-based pain coping skills training
Participation in this program is low risk. A few people may experience temporarily increased stress, anxiety and feelings of 'discomfort' (less than 10 people out of 100).

Risks from Interviews or questionnaires
- You may get tired or bored when we are asking you questions or you are completing questionnaires.
- The interviews and questionnaires may cause you stress and fatigue. Tell study staff if you feel uncomfortable during interviews or study visits. You do not have to answer any question you do not want to answer.
- You may discontinue your study participation if you do not wish to carry out further interviews or questionnaires.

Risks from Physical Exam
Measurement of vital signs and body measurements may cause psychological distress.

Risks from Best Practices
Risks are minimal. If a **Best Practice** causes you physical pain or discomfort, stop the activity and report the incident to a study team member. Other options may be possible.

Risk from Out-of-Pocket-Payment
This study will not cover costs for any prescribed treatment, including the Best Practice treatments you and your physician select. Your out-of-pocket payment for any prescribed treatment may depend on insurance coverage or the available treatments in your area, and will differ based on the treatment group you are assigned to.

Risk from Sharing Data

Even though we will protect your privacy as much as possible, there is a very small chance that the data could be identified as yours. The risk of this happening is very small, but may increase in the future as technology changes.

We will try to respect your privacy and protect your confidentiality throughout the study. We do this by keeping your tracking information (name, medical record number, address, and phone number) separate from your study file. In your study files, you are identified by a study ID number. We also share the information gathered in the study only with the people who need to know this information. However, there is the risk that psychological, emotional, financial, social, and legal risks might result if this confidentiality cannot be maintained.

Your study data will be stored securely at the study site and sent to data centers selected by the NIH to coordinate the study. At the end of the study, the data will be stored indefinitely by the NIH or a data center selected by the NIH to enable future research use. Your name and other personally-identifying information will not be kept with the final research data.

This study is part of the NIH HEAL Initiative focused on understanding and developing new treatments for addiction and pain. Research gives us the best information and progresses more quickly when data is available from many studies and many individuals, and when many researchers can work with the data and analyze them in different ways. Therefore, your data will be used for this and other NIH HEAL Initiative studies. Your stored data will also be made widely available to other researchers. The shared data may be used indefinitely for research not related to this study or the HEAL Initiative, without asking you for additional consent.

Please see the **"Site-Specific Consent Information"** (Part 2 of this consent), and the section or separate form on *HIPAA Authorization for Disclosure of Protected Health* Information for other details on how your privacy will be protected.

Unknown risk

There may be side effects and discomforts that are not yet known.

6. Are there risks related to pregnancy?

Due to the unknown effect of duloxetine in pregnancy, women who are pregnant or lactating are not be included in this study. If you become pregnant while in the study, please tell us; we will stop your treatment but ask that you continue completing follow-up assessments.

7. Are there benefits to being in the study?

You may or may not benefit from being in this study. You may or may not have less knee pain or learn how to better manage your pain.

If you take part in this study, you may help others in the future by helping us determine safe and effective ways to manage KOA without surgery.

There is no direct benefit to you from the storage and sharing of your data but sharing may help researchers learn more about knee osteoarthritis pain management, addiction and other diseases, which may help you or others in the future.

8. What are your options if you do not want to be in the study?

You do not have to join this study. If you would like to discuss Phase 2 of this study, please let a study team member know. Other options include routine care from your healthcare provider. Please discuss alternative care options with your healthcare provider.

If you do not join, your care at the study site will not be affected.

9. Will it cost you anything to be in this study?

Your insurance carrier will determine coverage for best practices and duloxetine. You will be responsible for insurance copays or services and medications not covered by your insurance. We will obtain your insurance information and give you an estimate of your cost responsibilities prior to study intervention.

The study will provide access to the online pain coping system free of charge for those in that group.

If you have billing or insurance questions contact your study doctor or the contact listed in the site-specific section located below.

10. Will you be paid if you join this study?

You will be paid $20 (twenty US dollars) for the online pre-visit questionnaire. For the baseline virtual or in-person visit, you will be paid $100.00 (one hundred US dollars). For the study visit at 4 weeks, you will be paid $20.00 (twenty US dollars). For the study visit at 8 weeks, you will be paid $100.00 (one hundred US dollars). For each monthly online/telephone questionnaire completed after the study visit at 8 weeks, you will be paid $5.00 (five US dollars). This compensation will be in the form of either cash, check or gift card.

For parking or travel to attend in-person study visits, we will provide you with a parking sticker, voucher or reimbursement in the form of either cash, a check or a gift card.

You may be required to provide your social security number to be paid for taking part in this study. Federal tax law requires that you report your research payments when you file your taxes. If your total payments from your study site exceed $600 per year, the study site will report these payments to the Internal Revenue Service and you will receive a 1099-MISC form.

See the site-specific section below for more information on payments.

11. Can you leave the study early or withdraw?

- You can agree to be in the study now and change your mind later.
- If you wish to stop or withdraw, please tell us right away.
- Leaving early will not stop you from getting regular medical care.

If you leave the study early, the study researchers may use or share your health information that it has already collected if the information is needed for this study or any follow-up activities. Even if you stop early or withdraw from the study, your information may be used to look at public records or national databases that record births and deaths for vital status. These public records may be reviewed if the study team was not able to reach you during the duration of the study.

Stopping duloxetine abruptly may result in irritability, nausea, dizziness, vomiting, headache or prickling sensations on the skin. To reduce these risks, a study team member or your healthcare provider should oversee the gradual withdrawal of duloxetine.

12. Why might we take you out of the study early?

You may be taken out of the study if:

- Staying in the study would be harmful.
- You fail to follow instructions.
- You become pregnant.
- The study is cancelled.
- There may be other reasons to take you out of the study that we do not know at this time.

If you are taken out of the study early, the study researchers may use or give out your health information that it has already collected if the information is needed for this study or any follow-up activities

13. Will the study require any of your other health care providers to share your health information with the researchers of this study?

The researchers may ask to see your health care records from your other health care providers. This may include your primary care provider, pain clinic, or orthopedic clinic. In addition, we may ask for copies of your knee imaging (x-ray, CT, or MRI) and the radiology written report.

14. What is a Certificate of Confidentiality?

Your study information is protected by a Certificate of Confidentiality that helps keep your information private when stored in the U.S. This Certificate allows us, in some cases, to refuse to give out your information even if requested using legal means.

It does not protect information that we have to report by law, such as child abuse or some infectious diseases. The Certificate does not prevent us from disclosing your information if we learn of possible harm to yourself or others, or if you need medical help.

Disclosures that you consent to in this document are not protected. This includes putting research data in the medical record or sharing research data for this study or future research. Disclosures that you make yourself are also not protected.

15. What other things should you know about this research study?

During the study, we will tell you if we learn any new information that might affect whether you wish to continue to participate.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time. If you would like to review the information for this study, or a summary of the results, ask the study team doctor for the ClinicalTrials.gov study registration number.

What is the Institutional Review Board (IRB) and how does it protect you?

This study has been reviewed by an Institutional Review Board (IRB), a group of people that reviews human research studies. The IRB can help you if you have questions about your rights as a research participant or if you have other questions, concerns or complaints about this research study.

For this multi-site study, Johns Hopkins has agreed to serve as the single IRB (sIRB) providing oversight for all sites. You may contact the Johns Hopkins IRB at 410-502-2092 or jhmeirb@jhmi.edu with your questions or concerns.

What should you do if you have questions about the study, or are injured or ill as a result of being in this study?
Call the principal investigator for your study site, which is listed in the **"Site-specific Consent Information"** (Part 2 of this consent).

If you have an urgent medical problem or think you are injured or ill because of this study, call 911 or go to your local emergency department.

If you wish to contact the overall study principal investigator(s), use the contact information provided on page one of this consent form.

16. Optional Study Components:

This part of the consent form is about optional component(s) of the study that you can choose to take part in or not. You can still take part in the main study even if you say "no" to this/these optional component(s).

Future Contact
We would like your permission for our research team to contact you in the future. Please note that your decision below does not prevent other researchers at your study site from contacting you about other research.

Please sign and date your choice below:

YES ☐ _____ _____
Signature of Participant Date

NO ☐ _____ _____
Signature of Participant Date

A Sequenced Strategy for Improving Outcomes in People With Knee Osteoarthritis Pain

Master Consent Form Phase 2 Version 2.5

NCT04504812

December 6th, 2022

Participant Study ID _____

RESEARCH PARTICIPANT INFORMED CONSENT AND PRIVACY AUTHORIZATION FORM

Protocol Title: A sequenced strategy for improving outcomes in people with knee osteoarthritis pain (SKOAP)

Phase 2 Consent

JHM IRB Application No.: IRB00238678

Version Number and Date: Version 2.5 December 6th, 2022

Sponsor/Supporter/Funded By: National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

Principal Investigator: Steven Cohen, MD
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Phone: 410- 955-1822
SKOAPStudy@jh.edu

See "Study Site Information" at the end of this consent form for contact information for your local study team.

You are being asked to join a research study. Participation in this study is voluntary. Even if you decide to join now, you can change your mind later.

This study is a multi-site study, meaning it will take place at several different locations. Because this is a multi-site study, this informed consent form includes two parts. The first part has information that applies to all study sites. The second part has information for the place where you are being asked to enroll.

1. Research Summary (Key Information):

The information in this section is intended to be an introduction to the study only. Complete details of the study are listed in the sections below. If you are considering participation in the study, the entire document should be discussed with you before you make your final decision. You can ask questions about the study now and at any time in the future.

This study compares different non-surgical treatments for knee pain caused by osteoarthritis. There are 2 phases in the study. Today we will discuss Phase 2 of the study.

People who enrolled in Phase 1 of SKOAP may join. People who did not want to participate in Phase 1, but are interested in Phase 2 may join.

For people who enroll in Phase 2, a computer will determine in which of the following 3 groups you will be placed:

- **Joint injection.** People assigned to receive this will have hyaluronic acid mixed with depo methylprednisolone (a steroid) and bupivacaine (an anesthetic) injected into the knee.

- **Nerve Blocks.** People assigned to receive this will have a long-acting local anesthetic (a.k.a. liposomal bupivacaine or EXPAREL) injected into the knee, followed by a steroid.

- **Nerve Ablation.** People assigned to receive this will have heat applied to destroy the nerves signaling pain in the knee, followed by a steroid.

If you receive one of the two nerve procedures (Nerve Block or Nerve Ablation), you will be blinded (you will not know) which procedure you received.

As part of the study, you will come to the clinic for the procedure. You will have a telemedicine visit with your physician or return to the clinic if required at four (4) and twelve (12) weeks after that visit. In addition to the study visits, you will be sent an online survey at eight (8) weeks to ask about your progress. After your last study visit at week 12, we will contact you every three months for one year.

You will complete a confidential contact form and you will to choose if you prefer to be contacted and complete follow-ups by text, email, online, or by telephone. This form will ask for contact information for you, your family members, or close friends to whom you give permission to respond to us in the event you are unable to do so. If you are unable to complete follow-up by your primary choice, you may be contacted by the Duke Clinical Research Call Center (the DCRI Call Center). There are risks to the study procedures and the study drugs that are described later in this document.

2. Why is this research being done?

This research is being done to compare treatments for knee osteoarthritis pain.

Knee osteoarthritis (KOA) occurs when the cartilage that cushions your knee joint wears down over time or from trauma. Symptoms of KOA include pain, swelling, tenderness, stiffness, and loss of flexibility in the knee. In this study, we are comparing non-surgical treatments in an effort to lessen your pain and improve knee function. To compare study treatments, some participants will receive a nerve ablation (have heat applied to destroy the nerve signaling pain in the knee) and others will receive a 'sham' nerve ablation (needles inserted close to pain nerves, but heat not applied so nerves should not be destroyed).

Are there any investigational drugs/devices/procedures?

Nerve blocks and nerve ablations are well accepted, common practice treatments for knee pain associated with osteoarthritis. The product we plan to use in the nerve block procedure has longer lasting effects. Although new, it is frequently used and has Food and Drug Administration (FDA) approval for use by local infiltration and nerve blocks for pain after surgery. The FDA has approved the use of this

drug in our study and the drug itself will be provided free of charge. Joint injection (of hyaluronic acid) is also FDA approved. Research suggests that combining it with a steroid and local anesthetic has better results.

People in this study may receive tramadol, an opioid-like pain reliever used to treat moderate to severe pain. Tramadol has FDA approval for joint pain management, such as that with KOA. You will decide with the study clinician whether tramadol is a good option for you. It is not used as an experimental medication in this study. If tramadol is not right for you, you may be prescribed a different FDA approved opioid medication. You and the study provider will make a shared decision about this.

Who can join this study?

People 18-90 years of age with knee pain due to osteoarthritis, and without knee replacement of the painful knee joint, may join. Study participants will need to be comfortable using a computer for simple tasks.

How many people will be in this study?

This is a multicenter study. We anticipate 900 to 1200 participants will be enrolled in Phase 2. About 300-400 people will enroll in each of the three groups.

3. What will happen if you join this study?

If you agree to be in this study, we will ask you to do the following things:

Pre-Intervention Visit

During this visit, you will review and provide a written informed consent. By signing, you are providing your permission to allow our study team to access to your medical records. This information will include x-rays, CT, or MRI scans, as well as other details from your medical record.

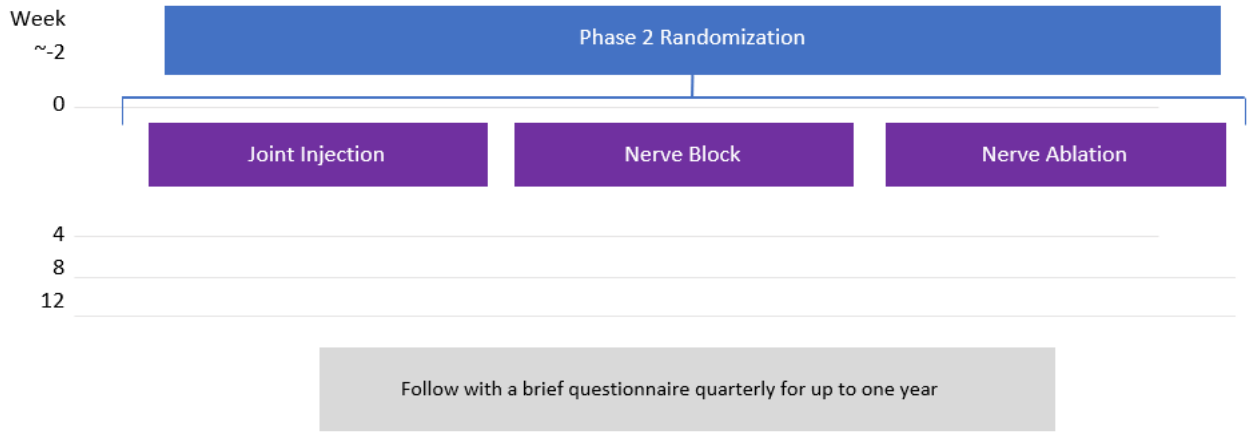
We will ask questions about your pain, medications (including opioid use), drug allergies, and contraindications for tramadol, or another opioid, and any of the study procedures.

A brief examination of the affected knee will be performed by a member of the study team.

A urine sample may be collected for toxicology and in women of childbearing potential, pregnancy testing, as a part of standard of care. Women who can bear children will be asked to confirm they will use reliable birth control.

The pre-intervention visit will take approximately 1-2 hours.

You will be randomized (like drawing numbers from a hat) and then assigned into one of the three groups as listed below. You will have an equal chance of being assigned to any of the three study groups.



If appropriate, you will be prescribed tramadol, up to two tablets per day (or the equivalent dose of another opioid) as needed.

Baseline Intervention Visit

The baseline visit will be the visit at which you receive one of the interventions, as described below.

We will ask questions concerning your medical history, general health, pain, physical function, and how you feel mentally or emotionally. In addition, we will again ask questions about your medications (including opioid use), drug allergies, and contraindications for tramadol, or another opioid, and any of the study procedures. You may also be asked to provide a urine sample to test for pregnancy and substance use.

- *Joint Injection Group*
  If assigned to this group, you will receive an injection of medications into the knee joint. For the joint injection, you may be positioned on your back, face up, with the knee flexed and resting on pillows or in a sitting position. Local numbing medication will be injected by needle into the skin. Hyaluronic acid (HA) mixed with a steroid and an anesthetic will be injected into the joint space. X-rays or ultrasound may be used to confirm correct placement of the injection. The total time for the entire visit will take approximately 30-60 minutes. After the procedure, you will be moved to the recovery area. Participants who respond well to the joint injection at the 12-week follow-up may be eligible to receive subsequent joint injections, not to exceed 4 injections per year.

- *Nerve Blocks*
  If assigned to this group, you will receive either a long-acting nerve block with local anesthetic and a steroid (if your doctors feels it is warranted), or a nerve ablation which is heat lesioning of targeted genicular nerves and then administration of a steroid. To make the procedure more comfortable, you may be offered sedation with low-dose midazolam (a short-acting sedative) or fentanyl (an opioid medication), on an 'as-needed' basis. People who respond well to the nerve block at the 12-week follow-up may be eligible to receive additional nerve blocks, not to exceed 4 nerve blocks per year.

- *Nerve Ablation*
  Some people will have nerve ablation. Nerves will be burned by an electrical current produced by radio waves to heat up a small area of nerve tissue, decreasing the pain signals from that area of the knee supplied by the nerve. After the procedure, a steroid will be injected around the nerves to minimize the risk of nerve inflammation and pain from the procedure. People who respond well to the nerve ablation can have the procedure repeated at 6 months.

  If you are assigned to one of the nerve groups, you will lie on your back, face up, with the knee bent and resting on pillows. After cleaning the skin with antiseptic, local numbing medication will be injected by needle into the skin. Your doctor will insert specialized needles (needles that also serve as electrodes) in up to 9 spots where we believe the nerves that transmit knee pain are located, and may use electrical stimulation to make sure we are close enough to the nerves for the treatment to work. This may feel like "tingling" or "pressure", but should not hurt. X-rays may be used to confirm correct placement of the needle and electrodes. These nerve procedures will take approximately 45-60 minutes. After the procedure, you will be moved to the recovery area.

  You will not know and the study physician or research staff will not tell you which of the 2 nerve treatments you received. If you seek emergency treatment at the site where your study treatment was done, your doctors will be able to see what treatment you received, if necessary, by looking in your medical chart.

  If you seek emergency treatment at a different site than where you received your study treatment and you or your doctor need to know which treatment you received, you or your doctor can call 888-216-1936 to leave a message and a call back number for Dr. Cohen, the PI of the SKOAP Study. Your message will be sent to Dr. Cohen automatically and Dr. Cohen or another investigator from the study will contact you ASAP.

No matter which treatment you receive, you may be prescribed tramadol for breakthrough pain, and will be followed for 12 months. Any additional procedures that are requested after the 12-week outcome visit will not be considered a study procedure. Additional joint injection, nerve blocks or nerve ablation will be considered clinical care and conducted as available and appropriate outside of the research study. If you decide to have an additional procedure, the physician or research staff will tell you which treatment you received so you may check your insurance coverage.

Follow Up Visits

Subsequent Visits
We will ask you to complete a phone call, telemedicine visit at four (4) weeks and twelve (12) weeks, or complete an in-person clinic visit if needed. We will ask you about your pain level, medication use, etc. We will also ask you to complete questionnaires related to pain, other symptoms, sleep, fatigue, and how you feel emotionally and mentally. The 4-week visit will take approximately 30 minutes. The 12-week visit will take approximately 60 minutes and you will complete additional questionnaires. The study clinician may adjust the dose of medications at the 12-week visit.

Online Check-ins
At 8 weeks we will ask you to complete an online questionnaire about your pain. This will take approximately 10 minutes.

Quarterly Follow-up Check-ins

After the 12-week visit, we will contact you every three months according to your choice of an online survey, text, email or telephone. You will be asked questions related to how you feel and any current therapy or surgery related to your knee osteoarthritis. These follow up contacts take approximately 10 minutes. You will be done at one year.

If your preference is to be contacted by phone, you will be contacted primarily by phone, but may also be contacted by email or postal mail by trained research staff from the Duke Clinical Research Institute Call Center (the DCRI Call Center) if you choose to be contacted quarterly by phone, or if you miss a text/online follow-up. The research staff will call you on the numbers you provided. Once enrollment is completed at your site, your site may close. If so, you may be followed by the DCRI Call Center. You will be notified if your site closes.

Will research test results be shared with you?

We will share with you only results that may impact your medical care, such as the results of your pregnancy test.

How long will you be in the study?

You will be in phase 2 of this study for at least 15 months, with 4 study visits and 5 online check-ins.

4. What happens to data that are collected in the study?

Our research team works to advance science, clinical practice, policy and public health. The data we collect about you are important to this effort.

If you join this study, you should understand that you will not own your research data. If researchers use your data to create a new product or idea, including those that may have commercial value, you will not benefit financially from those efforts.

How will your data be shared now and in the future?

Sharing data is part of research and may increase what we can learn from each study.

Often, data sharing is required as a condition of funding or for publishing study results. It also is needed to allow other researchers to validate study findings and to further research
Your data may be shared:

- Johns Hopkins University, as the core study team
- University of Utah, as the study database manager
- Duke University, as the clinical coordinating center
- Duke Clinical Research Institute Call Center
- research collaborators, other researchers, sponsors, government agencies, publishers of papers and other research partners
- federal government or other databases/repositories

Data sharing could change over time, and may continue after the study ends.

We will do our best to protect and maintain your data in a safe way. An Institutional Review Board (IRB) is a group of people that reviews human research studies. Generally, if we share your data without identifiers (such as your name, address, date of birth) no further review and approval will be needed. If data are shared with identifiers, further Institutional Review Board (IRB) review and approval may be needed. The IRB will determine whether additional consent is required.

The use of your data is required for participation in this research study. If you are not comfortable with the use of your data in future research without further consent, you should not participate in this study.

5. What are the risks or discomforts of the study?

There is a risk that you may be randomized to a study arm that is not as effective as you would like or not as effective as another arm offered in the study.

Risks from the joint injection itself (most common with hyaluronic acid)

Uncommon (1 to 5 in 100 people)

- Joint pain
- Injection site pain
- Joint swelling

Infrequent (less than 1 in 100 people)

- Joint stiffness
- Joint effusion (fluid)
- Arm or leg pain
- Synovitis (inflammation of the joint)
- Bruising
- Skin nodule or cyst
- Infection

Risks from depo-methylprednisolone (joint injection)

Uncommon (1 to 5 in 100 people)

- Headache
- Nausea and vomiting
- Swelling of ankles and feet

Rare (less than 1 in 1000 people)

- Allergic reaction (rash, itching, hives, swelling of tongue, lips, or face
- Cartilage loss (described only with multiple repeated injections)

Risks from lidocaine (local numbing)

Infrequent (less than 1 in 100 people)

- Redness at injection site
- Skin irritation

Risks from midazolam or fentanyl (sedation)

- Nausea or vomiting (less than 1 in 100 people)
- Disinhibition (lack of restraint) (less than 5 in 100 people)
- Prolonged sedation (sleepy for longer than 1 hour) (less than 5 in 100 people)
- Allergic reactions (about 3 in 1000 people)
- Serious complications such as respiratory compromise, myocardial infarction, stroke, **or death** (less than 1 in 10,000)

Risks from bupivacaine, Exparel® (nerve block)

- Occasional (less than 10 in 100 people) nausea

Rare (less than 1 in 1000 people)

- Allergic reactions (hives, itching, redness, throat welling, rapid heart rate, sneezing, fainting, excessive seating, low blood pressure)

Extremely Rare (less than 1 in 10,000)

- Central nervous system reactions (excitation, depression, restlessness, anxiety, dizziness, ringing in the ears, blurred visions, tremor, convulsions)
- Cardiovascular system reactions (heart block, arrhythmia, cardiac arrest, decreased blood pressure, death)
- Accidental intravascular injection (accidental injection into an artery or vein), which might cause failure to relieve pain or dizziness

Risks from tramadol (and other pain medications)

Common (5-20 in 100 people)

- Headache
- Dizziness
- Drowsiness
- Constipation
- Dry mouth

Risks from the joint injections, nerve blocks and nerve ablation

Occasional (less than 10 in 100 people)

- Patients with diabetes or glucose intolerance who receive steroids may experience elevated blood sugar for up to 48 hours. They will be informed of this risk, and instructed to test and adjust their hypoglycemic medications as indicated.

Uncommon (less than 5 in 100 people)

- Nerve ablation may result in procedure-related pain secondary to nerve inflammation, which may be reduced by use of steroids.
- Repeated intra-joint knee injections with steroids may increase the likelihood of cartilage loss.

Infrequent but serious (less than 4 in 1000 people)

- Nerve injury
- Infection (including osteomyelitis, a bone infection)
- Allergic reaction to bupivacaine (can cause rash, itching or difficulty bleeding- less than 1 in 1000)

Extremely rare (less than 1 in 10,000 people)

- Skin burns from nerve ablation, which are more common in thin individuals.

Risks from Fluoroscopy

Knee fluoroscopy is part of routine clinical care, and in this study it is being done to help the provider find specific locations for nerve treatments.

Risks from Interviews or questionnaires

- You may get tired or bored when we are asking you questions or you are completing questionnaires.
- The interviews and questionnaires may cause you stress and fatigue. Tell the staff if you feel uncomfortable during interviews or study visits. You do not have to answer any question you do not want to answer.

- You may discontinue your study participation if you do not wish to carry out further interviews or questionnaires.

Risks from Sharing Data
Measurement of vital signs and body measurements may cause psychological distress.

Risk from Out-of-Pocket-Payment
This study will not cover costs for any prescribed treatment. Your out-of-pocket payment for any prescribed treatment may depend on insurance coverage or the available treatments in your area, and will differ based on the treatment group you are assigned to.

Risk from the loss of confidentiality of sensitive information
Even though we will protect your privacy as much as possible, there is a very small chance that the data could be identified as yours. The risk of this happening is very small, but may increase in the future as technology changes.

We will try to respect your privacy and protect your confidentiality throughout the study. We do this by keeping your tracking information (name, medical record number, address, and phone number) separate from your study file. In your study files, you are identified by a study ID number. We also share the information gathered in the study only with the people who need to know this information. However, there is the risk that psychological, emotional, financial, social, and legal risks might result if this confidentiality cannot be maintained.

Your study data will be stored securely at the study site and sent to data centers selected by the NIH to coordinate the study. At the end of the study, the data will be stored indefinitely by the NIH or a data center selected by the NIH to enable future research use. Your name and other personally-identifying information will not be kept with the final research data.

This study is part of the NIH HEAL Initiative focused on understanding and developing new treatments for addiction and pain. Research gives us the best information and progresses more quickly when data is available from many studies and many individuals, and when many researchers can work with the data and analyze them in different ways. Therefore, your data will be used for this and other NIH HEAL Initiative studies. Your stored data will also be made widely available to other researchers. The shared data may be used indefinitely for research not related to this study or the HEAL Initiative, without asking you for additional consent.

Please see the **"Site-Specific Consent Information"** (Part 2 of this consent), and the section or separate form on *HIPAA Authorization for Disclosure of Protected Health* Information for other details on how your privacy will be protected.

Unknown risk
There may be side effects and discomforts that are not yet known.

6. Are there risks related to pregnancy?

Due to the use of radiation (fluoroscopy), women who are pregnant or lactating will not be included in this study. If you become pregnant while in the study and have already received the procedure, we will continue your participation through follow-up visits and check-ins as usual.

7. Are there benefits to being in the study?

You may or may not benefit from being in this study. You may or may not have less knee pain or learn how to manage your pain.

If you take part in this study, you may help others in the future by helping us determine safe and effective ways to manage KOA without surgery.

There is no direct benefit to you from the storage and sharing of your data but sharing may help researchers learn more about knee osteoarthritis pain management, addiction and other diseases, which may help you or others in the future.

8. What are your options if you do not want to be in the study?

You do not have to join this study. Other options include routine care from your healthcare provider. Please discuss alternative care options with your healthcare provider.

If you do not join, your care at the study site will not be affected.

9. Will it cost you anything to be in this study?

Your insurance carrier will determine coverage for all treatments. You will be responsible for insurance copays or services and medications not covered by your insurance.

We will obtain your insurance information and the clinic may give you an estimate of your cost responsibilities prior to study intervention.

If you have billing or insurance questions contact your study team or other contact listed in the site-specific section located below.

10. Will you be paid if you join this study?

You will be paid $20 (twenty US dollars) for the online pre-visit questionnaire. For the pre-intervention visit, you will be paid $20.00 (twenty US dollars). For the baseline intervention visit, you will be paid $100.00 (one hundred US dollars). For the study visit at 4 weeks, you will be paid $20.00 (twenty US dollars). For the online questionnaire at 8 weeks, you will be paid $10.00 (ten US dollars). For the study visit at 12 weeks, you will be paid $100.00 (one hundred US dollars). For each quarterly online/ telephone questionnaire after the study visit at 12 weeks, you will be paid $5.00 (five US dollars). This compensation will be in the form of either cash, check or gift card.

For parking or travel to attend in-person study visits, we will provide you with a parking sticker, voucher, or reimbursement in the form of either cash, a check or a gift card.

You may be required to provide your social security number to be paid for taking part in this study. Federal tax law requires that you report your research payments when you file your taxes. If your total payments from your study site exceed $600 per year, the study site will report these payments to the Internal Revenue Service and you will receive a 1099-MISC form from us.

See the site-specific section below for more information on payments.

11. Can you leave the study early or withdraw?

- You can agree to be in the study now and change your mind later.
- If you wish to stop or withdraw, please tell us right away.
- Leaving this study early will not stop you from getting regular medical care.

If you leave the study early, the study researchers may use or share your health information that it has already collected if it is needed for this study. Even if you stop early or withdraw from the study, your information may be used to look at public records or national databases that record births and deaths for vital status. These public records may be reviewed if the study team was not able to reach you during the duration of the study.

12. Why might we take you out of the study early?

You may be taken out of the study if:

- Staying in the study would be harmful.
- You fail to follow instructions.
- The study is cancelled.
- There may be other reasons to take you out of the study that we do not know at this time.

If you are taken out of the study early, the study researchers may use or give out your health information that it has already collected if the information is needed for this study or any follow-up activities.

13. Will the study require any of your other health care providers to share your health information with the researchers of this study?

The researchers may ask to see your health care records from your other health care providers. This may include your primary care provider, pain clinic, or orthopedic clinic. In addition, we may ask for copies of your knee imaging (x-ray, CT, or MRI) and the radiology written report.

14. What is a Certificate of Confidentiality?

Your study information is protected by a Certificate of Confidentiality that helps keep your information private when stored in the U.S. This Certificate allows us, in some cases, to refuse to give out your information even if requested using legal means.

It does not protect information that we have to report by law, such as child abuse or some infectious diseases. The Certificate does not prevent us from disclosing your information if we learn of possible harm to yourself or others, or if you need medical help.

Disclosures that you consent to in this document are not protected. This includes putting research data in the medical record or sharing research data for this study or future research. Disclosures that you make yourself are also not protected.

15. What other things should you know about this research study?

During the study, we will tell you if we learn any new information that might affect whether you wish to continue to participate. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time. If you would like to review the information for this study, or a summary of the results, ask the study team doctor for the ClinicalTrials.gov study registration number.

What is the Institutional Review Board (IRB) and how does it protect you?
This study has been reviewed by an Institutional Review Board (IRB), a group of people that reviews human research studies. The IRB can help you if you have questions about your rights as a research participant or if you have other questions, concerns or complaints about this research study.

For this multi-site study, Johns Hopkins has agreed to serve as the single IRB (sIRB) providing oversight for all sites. You may contact the Johns Hopkins IRB at 410-502-2092 or jhmeirb@jhmi.edu with your questions or concerns.

What should you do if you have questions about the study, or are injured or ill as a result of being in this study?
Call the principal investigator for your study site, which is listed in the **"Site-specific Consent Information"** (Part 2 of this consent).

If you have an urgent medical problem or think you are injured or ill because of this study, call 911 or go to your local emergency department.

If you wish to contact the overall study principal investigator(s), use the contact information provided on page one of this consent form.

16. Optional Study Components:

This part of the consent form is about optional component(s) of the study that you can choose to take part in or not. You can still take part in the main study even if you say "no" to this/these optional component(s).

Future Contact
We would like your permission for our research team to contact you in the future. Please note that your decision below does not prevent other researchers at your study site from contacting you about other research.

Please sign and date your choice below:

YES ☐ _____ _____
Signature of Participant Date

NO ☐ _____ _____
Signature of Participant Date